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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,046	09/16/2003	Scott E. Miller	B1102.70027US00	2591

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EXAMINER	
BOWERS, NATHAN ANDREW	
ART UNIT	**PAPER NUMBER**
1797	
MAIL DATE	**DELIVERY MODE**
11/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,046	MILLER ET AL.	
	Examiner	Art Unit	
	NATHAN A. BOWERS	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _19 August 2008_.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _34,35,41-44,46-50,53 and 81-96_ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _34,35,41-44,46-50,53 and 81-96_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 34, 35, 43, 44, 46, 47, 49, 50, 53, 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freeman (US 6653124) in view of Rao (US 20040121453) and Smith (US 6297046).

With respect to claims 34, 35 and 44, Freeman discloses an apparatus comprising a device having a predetermined reaction site (Figure 2:12) having a volume of less than 1

milliliter. This is described in column 1, lines 41-52 and in column 23, line 61 to column 24, line 48. Although Freeman does not describe the exact volume of the reactors, Freeman does indicate in column 1, lines 23-31 and throughout the reference that microfluidic bioreactors capable of accommodating nanoliter and microliter scale quantities are well known in the art. Column 24, lines 25-28 and column 29, lines 46-50 indicate that the apparatus comprises dissolved oxygen and pH measuring devices. Freeman, however, does not expressly disclose that the oxygen and pH sensors comprise a dye, a fluorescent molecule, or a chromogenic molecule.

Rao discloses a micro scale bioreactor comprising dissolved oxygen sensors that employ ruthenium based silicone rubber sensing films. The sensing films include a dye that serves to indicate varying oxygen concentrations in the reactor. This is disclosed in paragraphs [0100]-[0108].

Freeman and Rao are analogous art because they are from the same field of endeavor regarding microfluidic bioreactors.

At the time of the invention, it would have been obvious to utilize dissolved oxygen sensors that employ a dye in the bioreactor of Freeman. In paragraphs [0104] and [0106], Rao teaches that ruthenium dyes are advantageous because they may be incorporated into films that are easily attached to the interior bioreactor wall. Ruthenium dye based sensors are also advantageous because their measurements are equilibrium based and do not consume oxygen.

The combination of Freeman and Rao still differs from Applicant's claimed invention. Although Freeman does teach that the reactor comprises a semipermeable membrane (Figure

3:40) defining at least one wall of the reaction site, Freeman does not teach the relative permeabilities of oxygen and water vapor.

Smith discloses a culture vessel constructed from a polymer semipermeable membrane material (Figure 2:14 and Figure 2:12). Cells are grown within the vessel, and critical gases and water vapor are allowed to permeate the vessel walls. Column 4, lines 49-67 state the carbon dioxide and oxygen are allowed to diffuse through the walls at a fixed rate, and that water vapor is also allowed to permeate the walls, but at a reduced rate.

Freeman and Smith are analogous art because they are from the same field of endeavor regarding cell culture systems that utilize semipermeable membranes.

At the time of the invention, it would have been obvious to ensure that the membrane material utilized by Freeman is capable of allowing the permeation of water vapor at one order of magnitude lower than the permeation of oxygen. In column 24, line 56 to column 25, line 2, Freeman does place on emphasis on using the membrane to control the rate at which nutrients and gases are exchanged. For instance, Freeman states that “the membrane 40 may, for example, separate fluids on one side and oxygen and nutrients, sample reagents, or carbon dioxide on the other side." Thus, it can be inferred that the membrane provides for diffusion of water vapor and oxygen at different rates. Smith is evidence that polymer materials are well known in the art that allow for the diffusion of both water vapor and oxygen, such that water vapor is allowed to permeate at a much lower rate. It would have been obvious to ensure that the Freeman membrane is similarly situated so that it allows for the diffusion of oxygen to the growing cells, but is relatively restrictive of the passage of water vapor.

With respect to claim 43, Freeman, Rao and Smith disclose the apparatus in claim 34 wherein a plurality of reactors (12) are present. This is disclosed by Freeman in Figures 1 and 2.

With respect to claims 46 and 81, Freeman, Rao and Smith disclose the apparatus in claim 34 wherein at least one surface of the predetermined reaction site comprises a polymer. Column 16, line 44 to column 17, line 30 of Freeman indicates that polymer and copolymer adhesive layers are added to the microchambers. Column 10, lines 39-50 state that the surfaces of the reaction area are coated with proteins to facilitate cell binding. Column 14, lines 20-32 state that the reaction sites are constructed from polyesters and/or polyethylenes.

With respect to claims 47 and 82, Freeman, Rao and Smith disclose the apparatus in claim 34 wherein the living cell is either a mammalian or insect cell. The apparatus of Freeman is fully capable of culturing these cell types. Throughout the reference, Freeman describes drug testing by providing cell-based screening, so it can safely be assumed that the device is especially geared towards the culture of human tissue cells.

With respect to claims 49, 50 and 53, Freeman, Rao and Smith disclose the apparatus in as previously described above. In addition, Freeman teaches in column 29, lines 46-50 that it is known in the art to monitor temperature during cell culturing procedures.

2) Claims 41, 42 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freeman (US 6653124) in view of Rao (US 20040121453) and Smith (US 6297046) as applied to claim 34, and further in view of Kapur (US 6548263).

Freeman, Rao and Smith disclose the apparatus set forth in claim 34 as set forth in the 35 U.S.C. 103 rejections above. The Freeman reference teaches the use of sensors and detectors, and therefore implies that a control system is utilized for regulating system parameters. Freeman, however, does not expressly disclose the use of a processor for managing data obtained by the sensors.

Kapur discloses a microfluidic substrate for culturing and screening cells. Column 7, lines 63-67, column 26, lines 1-5, and column 39, line 60 to column 40, line 25 state that a controller, sensors, and associated actuators are provided for regulating temperature, oxygen content, and carbon dioxide content during cellular growth.

Freeman and Kapur are analogous art because they are from the same field of endeavor regarding microfluidic cell culture systems.

At the time of the invention, it would have been obvious to ensure that the microfermenter of Freeman was in communication with control systems capable of regulating dissolved oxygen content, pH, and temperature. Freeman indicates that the use of sensors capable of determining various environmental factors is well known in the bioreactor art. By providing an linked control system, one would have been able to monitor and manage the bioreactor automatically, and thereby increase the efficiency of the operation.

3) Claims 83, 84, 87-91 and 93-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freeman (US 6653124) in view of Rao (US 20040121453), Smith (US 6297046) and Barbera-Guillem (US 6455310).

With respect to claims 83, 84, 88, 95 and 96, Freeman, Rao and Smith disclose the apparatus set forth in the 35 U.S.C. 103 rejections above. Rao discloses the use of a fluorescent molecule, rather than chromogenic molecules, to detect the presence of oxygen in a culture medium.

Barbera-Guillem discloses a cell culture apparatus comprising a chamber (Figure 9:40) for growing cells. Barbera-Guillem teaches in column 10, lines 14-28 that chromogenic molecules are added to the chamber, and are capable of inducing a color change in response to an environmental factor. Barbera-Guillem teaches that detection of the color change is an easy way to recognize changes to various factors (such as pH) within the sample solution.

Freeman and Barbera-Guillem are analogous art because they are from the same field of endeavor regarding microfluidic bioreactors.

At the time of the invention, it would have been obvious to add a detection mechanism based on the presence of a chromogenic molecule to the fluorescence detection system disclosed by Freeman and Rao. In column 10, lines 14-28, Barbera-Guillem teaches that chromogenic detection systems are well known in the art, and are beneficial because they produce a color change that can be detected either by eye or by using a photodetector.

With respect to claim 87, Freeman, Rao, Smith and Barbera-Guillem disclose the apparatus in claim 83 wherein a plurality of reactors (12) are present. This is disclosed by Freeman in Figures 1 and 2.

With respect to claims 89 and 90, Freeman, Rao, Smith and Barbera-Guillem disclose the apparatus in claim 83 wherein at least one surface of the predetermined reaction site comprises a polymer. Column 16, line 44 to column 17, line 30 of Freeman indicates that polymer and copolymer adhesive layers are added to the microchambers. Column 10, lines 39-50 state that the surfaces of the reaction area are coated with proteins to facilitate cell binding. Column 14, lines 20-32 state that the reaction sites are constructed from polyesters and/or polyethylenes.

With respect to claims 91 and 94, Freeman, Rao, Smith and Barbera-Guillem disclose the apparatus in claim 83 wherein the living cell is either a mammalian or insect cell. The apparatus of Freeman is fully capable of culturing these cell types. Throughout the reference, Freeman describes drug testing by providing cell-based screening, so it can safely be assumed that the device is especially geared towards the culture of human tissue cells.

With respect to claim 93, Freeman, Rao, Smith and Barbera-Guillem disclose the apparatus in claim 83. In addition, Freeman teaches in column 29, lines 46-50 that it is known in the art to monitor temperature during cell culturing procedures.

4) Claims 85, 86 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freeman (US 6653124) in view of Rao (US 20040121453), Smith (US 6297046) and Barbera-Guillem (US 6455310) as applied to claim 34, and further in view of Kapur (US 6548263).

Freeman, Rao, Smith and Barbera-Guillem disclose the apparatus set forth in claim 34 as set forth in the 35 U.S.C. 103 rejections above. Freeman teaches the use of sensors and detectors, and therefore implies that a control system is utilized for regulating system parameters. Freeman, however, does not expressly disclose the use of a processor for managing data obtained by the sensors.

Kapur discloses a microfluidic substrate for culturing and screening cells. Column 7, lines 63-67, column 26, lines 1-5, and column 39, line 60 to column 40, line 25 state that a controller, sensors, and associated actuators are provided for regulating temperature, oxygen content, and carbon dioxide content during cellular growth.

Freeman and Kapur are analogous art because they are from the same field of endeavor regarding microfluidic cell culture systems.

At the time of the invention, it would have been obvious to ensure that the microfermenter of Freeman was in communication with control systems capable of regulating dissolved oxygen content, pH, and temperature. Freeman indicates that the use of sensors capable of determining various environmental factors is well known in the bioreactor art. By providing a linked control system, one would have been able to monitor and manage the bioreactor automatically, and thereby increase the efficiency of the operation.

Response to Arguments

The double patenting rejections over Application No. 10/664067 have been withdrawn.

Applicant's arguments filed 19 August 2008 with regard to the 35 U.S.C. 103 rejections involving Sheppard Jr. have been fully considered and are persuasive. Accordingly, these rejections have been withdrawn.

Applicant's arguments filed 19 August 2008 with regard to the 35 U.S.C. 103 rejections involving Freeman have been fully considered and are persuasive. However, upon further consideration, a new ground of rejection has been made in view of the combination of Freeman with Smith.

Smith addresses the deficiencies of Freeman by indicating that membrane materials are known in the art capable of regulating the permeability of oxygen and water vapor so that the permeability of water vapor is at least one order of magnitude lower than that of oxygen. One of ordinary skill in the art would have found it obvious to use the membrane materials – or other polymer materials characterized by similar properties – disclosed by Smith in the apparatus of Freeman in order to ensure that water vapor is permeated at a lower rate than oxygen. This is coordinate with Freeman's stated objective of keeping fluids predominantly on one side of the semi-permeable membrane.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan A. Bowers whose telephone number is (571) 272-8613. The examiner can normally be reached on Monday-Friday 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/William H. Beisner/
Primary Examiner, Art Unit 1797

/Nathan A Bowers/
Examiner, Art Unit 1797